REMARKS

The following is responsive to the office action of January 25, 2005.

Applicants appreciate the examiner's explicit withdrawal of various objections and rejections. With respect to these, applicants stand by their prior comments, if any. Applicants will not burden the record with any further discussion. However, said silence is not to imply necessarily agreement with any of the examiner's comments.

The rejection of paragraph 9 referring to the drawings is not understood. Reference is made to applicant's last reply which extensively clarified the description of the drawings. If the examiner has further specific objections, applicants will be happy to fix them.

With respect to the rejection of paragraph 10, relating to certain informalities relating to the sequences, as well as paragraph 15, applicants refer to their last reply, page 12, paragraph 3. A new copy of amended page 27 is attached. Note the last reply at the bottom of page 6 where the previous version of page 27 was canceled and replaced with the new page, now attached again. Also being filed herewith is another copy of the amendment of September 1, 2000 as the examiner requests.

The rejections and objections to claim 35 have been rendered moot by its cancellation. To the extent any of these apply to the amended version of claim 36, applicants have the following remarks.

Whereas there may not be a specific example which further mutates L19, the specification is replete with guidance as to how this could be done. In particular, the process would involve, for example, mutations analogous to those reported in example 2 from which the antibody E1 was modified to produce H10 which, in turn, was modified to produce L19. With this guidance, a skilled worker could prepare antibodies with an affinity less than 54pM. Note, *In re Wands858 F.2d 731, 8USPQ2d 1400 (Fed.Cir. 1988),* where a claim recited a monoclonal antibody having an affinity of at least 10^{-9} M^{-1}. Achievement of such antibodies was found enabled although preparation of such high affinity antibodies entailed "immunizing animals, fusing lymphocytes from the immunized animals with myeloma cells to make hybridomas, cloning the hybridomas, and screening the antibodies produced by the hybridomas for the desired characteristics." The

fact that such a large degree of experimentation was routine in the field and thus not undue, was determinative of the existence of enablement. The same is true for the claims of this application, especially in view of the guidance provided in the examples.

Lastly, the examiner alleges defects in various phrases which specify the number of mutations or which combine various affinity values in the specification to provide ranges in several claims. All of these phrases and ranges are fully supported under long standing case law. Thus, in *In re Voss, 557 F.2d 812, 194 USPQ 267 (CCPA 1977),* the Court stated at *194 USPQ 272, n14*:

> Even if we were to assume that the term "glass-ceramic material" encompassed materials with a crystal content as low as 20% by weight, description of the range 20-100% (100% being the theoretical upper limit of crystallinity) would necessarily describe the range 50%-100% crystal content now claimed unless the broad range pertained to a different invention from that involving the narrower range. *In re Wertheim.*

See also *In re Wertheim, 541 F.2d 247, 191 USPQ 90 (CCPA 1976).*

In *In re Blaser, 556 F.2d 247, 191 USPQ 90 (CCPA 1977)* the Court stated at *194 USPQ 125*:

> Appellants rely on the rationale of In re Wertheim, supra, as "clearly applicable here." Appellants urge that if a disclosure of 25-60% solids content taught those skilled in the art that 35-60% was part of the invention in Wertheim, although the latter range was not expressly mentioned therein, then appellants' disclosure of 60° C to 200° C in SN 159,159 would likewise teach 80° C to 200° C as part of appellants' invention. We agree with appellants that Wertheim is controlling on this point.

Consequently, it is clear that various numbers of mutations are supported by the specification. As the examiner indicates, the original phraseology of claim 6 ("limited number of mutations") and the precise locations of mutations in original claim 7 would indicate that at least up to 8 mutations can exist. This is a synonym for a number of mutations which is at least 1-8. Thus, the latter range is explicitly supported in the application. Under *Wertheim, Voss, Blaser,* etc. the range of at least 1-8 provides clear support for subsumed ranges such as 1-3 as well as individual values such as 1, 2, 3, etc. Similarly, the explicit mention of affinity values such as < $1x10^{-9}$ M, 54pM, 27pM, etc. provides support for the various recited ranges, such as 27-54pM (as in original claim 8 anyway), 0.027 to <$1x10^{-9}$ M, as well as ranges involving values falling

within the latter range.

The embedded hyperlinks, etc. were already cancelled from the specification in the amendment to figure 1 made on page 3 of the last reply. Thus, the objection in paragraph 14 of the office action is moot.

The double-patenting rejection of paragraph 16 is untenable. There already is a "clear line of demarcation" between claims 12-13 of the cited application and claim 20 of this application. The latter is drawn to a conjugate of an antibody and a molecule which induces blood coagulation and blood vessel occlusion. The former are drawn to radiolabeled antibodies without any mention of conjugation to a molecule as recited in claim 20 of this application. This clearly establishes the requested demarcation line.

As for the remaining rejection of paragraph 19, it is respectfully submitted that this should be withdrawn. The examiner alleges that various uses of "less than" modifying various affinities are not supported in the specification. This is not true. The concept that the invention is directed to antibodies having affinities "less than" various values is disclosed throughout the specification. For instance, in the very first sentence of the specification, reference is made to "antibodies with sub-nanomolar affinity." This clearly supports the concept of affinities "sub," i.e., "less than," nanomolar ($1x10^{-9}$ M). See also the fifth line from the bottom of page 4 in the summary of the invention, as well as the last sentence of the first full paragraph of page 8 of the application, for example.

Moreover, the specification repeatedly refers to antibodies of "improved" affinities. See, e.g., page 5, lines 3-6, page 8, lines 12-16, page 15, first sentence, and original claims 1 and 6. Improved affinity, of course, refers to affinities which are lower than that of a parent, i.e., "less than" that of the parent. Thus, the concept of providing antibodies having affinities less than parent antibodies is unambiguously disclosed in the application. Note further the last paragraph on page 7 of the specification more definitively discussing the concept of comparison with a parent, i.e., starting material antibody.

Furthermore, the entire specification is drawn to the concept of improving affinities, i.e., Kd values, over those which were in the prior art. Furthermore, in example 1 of the application, certain antibodies are prepared (E1, E2 and G4). In example 2, one of these (E1) is taken as a

new starting material for further improvement of affinity. This leads to antibody H10. The latter, in turn, becomes the starting material for further modifications (mutations) in antibody sequence which lead to a further improved antibody, L19. Thus, unambiguously this application is directed to providing antibodies having increased affinities which are "less than" the previous antibody in a sequence of experiments.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

Anthony J. Zelano, Reg. No. 27,969
Attorney for Applicant(s)

MILLEN, WHITE, ZELANO
& BRANIGAN, P.C.
Arlington Courthouse Plaza 1, Suite 1400
2200 Clarendon Boulevard
Arlington, Virginia 22201
Telephone: (703) 243-6333
Facsimile: (703) 243-6410

Attorney Docket No.: ELLIS-0002-P01

Date: February 27, 2006
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Table 1:

Sequences of selected anti-ED-B antibody clones

	VH chain			VL chain		
Clone	31-33*	50-54*	95-98*	32*	50*	91-96*
A2	SYA	AISGSG	GLSI	Y	G	NGWYPW
G4	SYA	AISGSG	SFSF	Y	G	GGWLPY
E1	SYA	AISGSG	FPFY	Y	G	TGRIPP
H10	SFS	SIRGSS	FPFY	Y	G	TGRIPP
L19	SFS	SIRGSS	FPFY	Y	Y	TGRIPP

Relevant amino acid positions (*: numbering according to Tomlinson et al. (1995) EMBO J., 14, 4628-4638) of antibody clones isolated from the designed synthetic libraries. Single amino acid codes are used according to standard IUPAC nomenclature.